UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/555,278	08/30/00	SVANBORG	C 032313-003

021839
BURNS DOANE SWECKER & MATHIS L L P
POST OFFICE BOX 1404
ALEXANDRIA VA 22313-1404

HM12/0911

EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	10

DATE MAILED: 09/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/555,270	Applicant(s) SVANBORG, CATHARINA
	Examiner Anne Holleran	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *15,16,18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The preliminary amendment filed May 26, 2000 (Paper No. 6) is acknowledged.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-14 and 17 in Paper No. 9 (filed June 25, 2001) is acknowledged. The traversal is on the ground(s) that the instant application is an international application that should have unity of invention standards applied for purposes of restriction between different classes of invention. This is not found persuasive because the standards for unity of invention were applied in Paper No. 7. The claims of group I are drawn to a product and a method of using the product. The claims of groups II and III are drawn to additional methods. Under the rules for unity of invention, the examiner is not required to search and examine additional methods of use of a claimed product. (see 37 CFR 1.475).

The requirement is still deemed proper and is therefore made FINAL.

Informalities

3. The specification is objected to because it lacks most of the appropriate section headings. Correction is required.

4. Claim 6 contains a typographical error: "cytoxin" should be amended to "cytotoxin"

Priority

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Claim Rejections - 35 USC § 112

6. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 provides for the use of an agent, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 14 is also rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

7. Claims 14 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating cancer with an agent of claim 1, where the agent is a multimeric α-lactalbumin conjugated with a targeting protein such as an antibody, does not reasonably provide enablement for methods of treating cancer with any agent within the scope of claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are : 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Claims 14 (interpreted as drawn to a method for the purposes of this rejection) and 17 are broadly drawn to methods of treating cancer comprising the administration of any agent within the scope of claim 1. The scope of claim 1 is extremely broad, and includes the combination of multimeric α-lactalbumin with any second reagent. The specification teaches examples of the second reagent, and these include toxins, labels, any type of protein, and antibodies. In addition, the scope of claim includes multimeric α-lactalbumin bound to calcium. The specification further teaches that multimeric α-lactalbumin is an apoptosis-inducing agent, and provides working examples to demonstrate that multimeric α-lactalbumin enters the nucleus of cancer cells and causes cell death via induction of apoptosis.

The specification fails to teach examples of in vivo experiments demonstrating effectiveness of multimeric α-lactalbumin for the treatment of cancer. It is well known that demonstration of cell death in vitro does not always correlate with efficacy in in vivo models (see Jain, R.K., Scientific American, 271: 58-65, 1994). Furthermore, Hakansson teaches that multimeric α-lactalbumin induces apoptosis in transformed and non-transformed cells lines, and that peripheral blood lymphocytes are sensitive to the effects of multimeric α-lactalbumin. Thus, it does not appear that multimeric α-lactalbumin by itself is a specific cytotoxin. Thus, without working examples demonstrating in vivo efficacy, the specification fails to establish that the claimed methods of treatment may be made and used by one of skill in the art in which any of the agents encompassed by claim 1 are used. While, specific targeting of multimeric α-lactalbumin with an antibody that specifically directs it to a tumor cell may be enabled by the specification, it is not clear that treatment of cancer comprising administering multimeric α-lactalbumin in combination with any second reagent is enabled by the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Sabharwal et al (WO 96/04920; published 22 February 1996; cited in IDS) as evidenced by Kuwajima (Kuwajima, K., FASEB Journal, 10: 102-109, 1996; cited in IDS).

Claim 1 is drawn to an agent comprising a protein complex comprising oligomeric α-lactalbumin (MAL) and a second reagent. Claims 11-13, dependent from claim 1, are drawn to pharmaceutical compositions. The pharmaceutical compositions may be in the form of a solution or cream, or adapted for oral administration.

Sabharwal teaches multimeric α-lactalbumin, which is a compound that binds calcium ion, as evidenced by the teachings of Kuwajima (see page 102, 2nd col.). Absent evidence to the contrary, it is assumed that when multimeric α-lactalbumin enters the nucleus, that the bound calcium is carried along with it into the nucleus. Thus, Sabharwal teaches an agent comprising a protein complex comprising multimeric α-lactalbumin and a second reagent. Sabharwal also teaches pharmaceutical compositions comprising multimeric α-lactalbumin (see page 20, line 1 – page 21, line 7). Thus, Sabharwal teaches the agent of claim 1 and the pharmaceutical compositions of claims 11-13.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) as evidenced by Kuwajima (Kuwajima, K., FASEB Journal, 10: 102-109, 1996; cited in IDS).

Hakansson teaches multimeric α-lactalbumin (see page 8065, 1st to 2nd column). As discussed above, multimeric α-lactalbumin is a calcium binding protein. Thus, Hakansson teaches an agent that is the same as that of claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ming (Ming, L.-J., Magnetic Resonance in Chemistry 31: S104-S109, 1993; cited in the IDS).

Claim 8, dependent from claim 1, is drawn to an agent where the second reagent is a labeling agent. Ming teaches the substitution of calcium ion with ytterbium ion. Ytterbium ion is considered to be a labeling agent because Ming teaches its use as a paramagnetic probe in NMR spectroscopy. Ming fails to teach multimeric α-lactalbumin complexed with ytterbium ion. However, because Ming teaches how to label α-lactalbumin with ytterbium ion, it would have been obvious to one of ordinary skill in the art at the time the invention was made how to label multimeric α-lactalbumin with ytterbium ion.

11. Claims 1-4, 6, 7, 11, 14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) in view of Blair and Ghose (Blair, A.H. and T.I. Ghose, J. of Immunological Methods, 59: 129-143, 1983).

Claims 2-4, dependent from claim 1, are drawn to agents where the second reagent is coupled to multimeric α-lactalbumin by conjugation, by covalent bonding or by way of a linking

or spacer group. Claims 6 and 7, dependent from claim 1, are drawn to agents where the second reagent is an antibody or a monoclonal antibody. Claims 14 and 17, dependent from claim 1, are interpreted as drawn to methods of treating cancer, where the multimeric α-lactalbumin is combined with a targeting antibody. Claim 14, a "use" claim, is, for the purposes of this rejection, interpreted as drawn to a method of treating cancer.

Hakansson teaches multimeric α-lactalbumin, and teaches that multimeric α-lactalbumin is a toxin to cancer cells and immature cells (see abstract). Hakansson fails to teach multimeric α-lactalbumin conjugated to a second agent, such as an antibody. However, it is well known in the art to conjugate cytotoxic agents to targeting molecules, such as antibodies, as taught by Blair and Ghose (see page 129, 1st paragraph). Blair and Ghose also teaches methods of covalently linking toxic agents to antibodies that result in the formation of linking groups between the toxic agent and the antibody (see Table II). In view of the well known methods of linking cytotoxic agents to antibodies and further in view of teachings of Blair and Ghose that the specificity of cytotoxic agents is improved by targeting using the specificity of antibodies, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the multimeric α-lactalbumin of Hakansson by conjugating it to an antibody by the methods taught by Blair and Ghose.

12. Claims 1, 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) in view of Puri et al (U.S. 5,614,191; issued Mar. 25, 1997).

Claim 5, dependent from claim 1, is drawn to an agent wherein the second reagent is comprises a polypeptide or protein which is fused to multimeric α-lactalbumin. Hakansson fails to teach multimeric α-lactalbumin as a part of a fusion protein fused to a second protein or polypeptide. However, it is well known in the art to create fusion proteins between cytotoxic agents and targeting agents to increase specificity of the cytotoxic agent. For example, Puri teaches how to make a fusion protein between a cytotoxic agent and an interleukin-13 receptor (see column 21, line 30 – column 22, line 29). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the multimeric α-lactalbumin of Hakansson by making it into a fusion protein as exemplified by Puri.

13. Claims 1 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hakansson et al (Hakansson, A. et al, Proc. Natl. Acad. Sci., USA, 92: 8064-8068, 1995; cited in IDS) in view of Johnstone and Thorpe (Immunochemistry in Practice, Blackwell Scientific Publications, Oxford, 1987; pages 113-130) and also in view of Goers (Goers, J. Immunochemical Techniques Laboratory Manual, Academic Press, New York, 1993; pages 69-79).

Claims 8-10, dependent from claim 1, are drawn agents where the second reagent is a labeling agent that may be a biotin or a radioactive label; the radioactive label may be ^{125}I, ^{14}C, or ^{35}S.

Hakansson teaches multimeric α-lactalbumin, but fails to teach multimeric α-lactalbumin in combination with a label. However, the labeling of proteins with radioactive labels or biotin is

well known in the art as evidenced by the teachings of Johnstone and Thorpe or Goers. Johnstone and Thorpe teaches radiolabeling of proteins and demonstrates how to radiolabel with ^{125}I, ^{14}C, or ^{35}S. Goers teaches labeling of antibodies and teaches how to label with biotin. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the multimeric α-lactalbumin of Hakansson to make a labeled agent as claimed.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
September 9, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600